Apathetic thyrotoxicosis

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Summary: Apathetic thyrotoxicosis is an atypical though not rare manifestation of hyperthyroidism. The cardinal features are apathy and depression, as opposed to hyperkinesis and mental alertness in the usual thyrotoxic patient, and are unassociated with the usual signs and symptoms of hyperthyroidism, making the diagnosis difficult. We report three cases of apathetic thyrotoxicosis seen during one year.

Résumé: *Thyréotoxicose apathique*

La forme apathique de la thyréotoxicose est une manifestation atypique de l'hyperthyroïdie, mais qui n'est cependant pas rare. Ses caractéristiques capitales sont l'apathie et la dépression, alors qu'une hypercinésie et une vivacité mentale sont d'observation courante chez le malade thyréotoxique. Ces symptômes d'apathie et de dépression ne sont pas accompagnés des signes et symptômes classiques de l'hyperthyroïdie, ce qui rend le diagnostic difficile. Nous rapportons ici trois cas de cette thyréotoxicose apathique qui ont été vus au cours d'une année.

In so-called "masked" or "hidden hyperthyroidism" atypical manifestations of thyrotoxicosis can occur, leading to diagnostic difficulties. This type of hyperthyroidism chiefly affects the heart, producing unexplained or refractory heart failure, arrhythmias, or sustained or paroxysmal atrial fibrillation, and is most common in the elderly. Severe gastrointestinal manifestations such as malabsorption or steatorrhea may occur, and to a lesser extent neuromuscular disorders such as chronic muscular weakness, fits and encephalopathy or a choreiform syndrome.[1] However, a careful history and thorough physical examination will reveal other features of thyrotoxicosis.[2]

An uncommon, though not rare, manifestation of hyperthyroidism is apathetic thyrotoxicosis.[3-6] In this condition the cardinal features are apathy and depression in contrast to the excitability and hyperkinesis of hyperthyroidism. In patients with this syndrome the usual signs and symptoms of thyroid overactivity are absent and diagnosis is delayed. Although these patients do not appear extremely ill the disease is far from mild and may terminate in apathetic crisis.[5] We wish to report three cases of apathetic thyrotoxicosis seen within a year, in which the diagnosis was unsuspected at the time of admission.

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Case reports

Case 1

A 59-year-old housewife gave a two-year history of anorexia, gradual weight loss, listlessness and lethargy. She had been unable to walk for the last six months because of extreme weakness. She had received treatment with diazepam and tricyclic antidepressants with no effect. No history of previous mental illness was elicited. One month prior to admission she had developed ankle edema and orthopnea. She was admitted to this hospital in mild congestive heart failure and for investigation for possible malignant disease.

The patient was depressed, uncommunicative and expressed a wish to die. She was afebrile and her skin was dry. She had sinus tachycardia, with a pulse rate of 130 beats/min. Blood pressure was 150/100 mm Hg. Marked weakness and wasting of the shoulder and pelvic girdle muscles and small muscles of the hands were noted. Thyroid function tests were ordered because of the tachycardia and refractory congestive heart failure. Serum thyroxine (T_4) level was 16 μg/dl (normal, 4.6 to 11.2 μg) and T_3 resin uptake was 44% (normal, 25 to 35%).

The patient was transferred to the endocrine service. No history of heat intolerance, change in bowel habit or other symptoms of hyperthyroidism were obtained. No hand tremor or ocular signs of hyperthyroidism were present. She had bilateral ptosis. The thyroid gland was not enlarged; this was confirmed by a thyroid scan. The 24-hour radioactive iodine (^{131}I) uptake was 74% (normal, 14 to 40%). The serum immunoreactive thyroid-stimulating hormone (TSH) level was unresponsive to a bolus injection of 200 μg of thyrotropin-releasing hormone (TRH).

She was treated with 6 mCi of ^{131}I-sodium iodide and discharged on carbimazole 60 mg daily in divided doses. Two weeks later the T_4 level and T_3 resin uptake had returned to normal. There was considerable improvement in mental status as well as some improvement in muscular strength. Carbimazole was discontinued after two further weeks. Six weeks later she relapsed with depression, apathy and generalized muscle weakness. The serum T_4 level at this time was 15 μg/dl and T_3 resin uptake 41%. She was given a further dose of ^{131}I-sodium iodide (7 mCi) and placed again on carbimazole. There followed marked improvement in her mental status. Three months after discontinuation of carbimazole she was euthyroid, no longer depressed or apathetic, and had gained 12 kg.

Case 2

This 63-year-old woman had lost 20 kg over 12 to 14 weeks. At the same time she had had ankle edema, polymyalgia and depression. On admission she had sinus tachycardia, with a pulse rate of 140 beats/min. Blood pressure was 130/70 mm Hg. A precordial systolic murmur was present. Marked weakness and wasting of the shoulder and pelvic girdle muscles and the small muscles of the hands were noted. A diagnosis of polymyalgia rheumatica was made and the patient discharged on prednisone and furosemide.

The results of routine thyroid function tests reached the attending physician only after the patient's discharge; because the serum T_4 level was 15 μg/dl and the T_3 resin uptake 48% she was readmitted for treatment. She admitted to decrease in alertness, easy fatiguability, listlessness and lack of interest in her environment. She was emaciated and appeared depressed. Her skin was cool and dry and there was no hand tremor, thyroid gland enlargement or ocular signs of thyrotoxicosis. Bilateral ptosis was present. She had marked muscular weakness and wasting as previously noted. The serum TSH level was unresponsive to an intravenous bolus of 200 μg of TRH.

She was treated with carbimazole 15 mg *tid* and after two weeks was no longer apathetic and depressed. She was subsequently treated with 6 mCi of ^{131}I-sodium iodide.

Case 3

A housewife aged 59 years gave a 10- to 12-week history of dyspnea on effort and depression. She appeared depressed and lethargic. She had sinus tachycardia, with a pulse rate of 130 beats/min. Blood pressure was 140/75 mm Hg. Apart from mild congestive failure and a dry skin the physical examination findings were within normal limits. The serum T_4 level was 28 μg/dl and the T_3 resin uptake 45%.

She was then transferred to the endocrine service. Her husband described an 18-week history of depression, irritability, forgetfulness, lack of former interest and lethargy. She had become virtually bed-

ridden because of fatigue and weakness. She had no past history or family history of mental illness.

She denied heat intolerance, diaphoresis, change in bowel habits or other symptoms suggestive of thyrotoxicosis. She had dry skin, bilateral ptosis, signs of heart failure and weakness and wasting of shoulder and pelvic girdle muscles and the small muscles of the hand. Radioactive iodine uptake was consistent with hyperthyroidism. The serum TSH level was unaffected by TRH administration, suggesting hyperthyroidism. No subjective improvement was felt by the patient up to 24 hours following TRH administration.

She was treated with 6 mCi of ^{131}I-sodium iodide and subsequently carbimazole 45 mg daily in divided doses. She was euthyroid six weeks after initiation of treatment, no longer apathetic or depressed and her muscular weakness was considerably improved.

Discussion

Apathetic thyrotoxicosis as a distinct entity was first described by Lahey[3,4] and subsequently by others.[5,6] The salient features of apathy and depression are associated with profound weight loss, proximal and distal muscle weakness and wasting, ptosis, dry skin, mild tachycardia and often congestive cardiac failure. Noteworthy is the absence of hyperkinetic motor activity, hand tremor and ocular signs typical of Graves' disease. The thyroid gland if palpable is minimally enlarged. This absence of the typical signs and symptoms of thyrotoxicosis may cause the diagnosis to be missed. It is important to emphasize this point since these patients under usual conditions do not appear extremely ill but under stress may "quietly and peacefully sink into coma and die an absolutely relaxed death without activation", unlike the classic thyrotoxic patient who goes into crisis.[3] Thus the disease may remain atypical throughout its course. Once this condition is suspected thyroid function tests will confirm the diagnosis. If apathetic thyrotoxicosis is strongly suspected clinically but conventional thyroid function test results are normal the physician should insist on radioimmunoassay of serum T_3 which will readily confirm the diagnosis.[7]

The pathogenetic events leading to a state of apathy and depression in these patients are not known. A widely held hypothesis is that in depression there is a deficiency of brain biogenic amines, primarily the catecholamines noradrenalin and dopamine.[8] In thyrotoxicosis there is a decrease in circulating catecholamines.[9] Insidious onset and delay in diagnosis of apathetic thyrotoxicosis may allow depletion of body stores of noradrenalin. Another possibility is unresponsiveness to catecholamines at the receptor level, which explains the ptosis noted in these patients.[2] However, a paradoxic improvement has been observed with adrenergic blockade in patients with apathetic crisis, though the ptosis remained unaffected.[6]

In general there is a lack of precise knowledge of the effect of thyroid hormones on the central nervous system. Recent evidence indicates that TRH has an immediate therapeutic antidepressant effect when administered to severely depressed euthyroid patients.[10] Studies indicate that TRH potentiates behavioural effects of levodopa and pargyline in mice and is equally active in hypophysectomized and intact animals, thus excluding a role for either TSH or thyroid hormones.[10] TRH may have a direct effect on the brain in alleviating depression either by increasing dopaminergic receptor sensitivity or altering the metabolism of dopa in such a way as to increase the concentration of active dopamine in the brain.[11] Only when methodology is sufficiently improved to permit measurement of circulating TRH and to detect abnormal reduction in blood levels will it be possible to know whether there is undue depletion of TRH in apathetic hyperthyroid patients. However, whether it is depletion of TRH or catecholamines, or unresponsiveness to the latter, that is implicated in the pathogenesis of mental apathy and depression in susceptible patients is speculative at this stage.

The three patients described had all the features of apathetic thyrotoxicosis but in the absence of typical signs and symptoms of thyroid overactivity the diagnosis was initially missed. We would like to emphasize that ptosis may be a valuable clue to the correct diagnosis. There was no subjective improvement in the patients' apathy or depression immediately or over the ensuing 24 hours after an intravenous bolus injection of 200 µg of TRH, the opposite of the beneficial response observed in euthyroid depressed patients. Furthermore, the TSH response to TRH in these patients was similar to that obtained in Graves' disease.

Its presence in 3 out of 20 patients hospitalized with thyrotoxicosis over a 12-month period would suggest that apathetic thyrotoxicosis is more common than is generally believed. Because this condition if untreated may be fatal, but if recognized responds gratifyingly to treatment, it is important that the physician be alert to the possibility of its presence in a depressed patient with the other signs displayed in our cases.

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